

JP 49-66660 A

## Description

## 1. Title of the invention

Process for asymmetric production of chrysanthemic  
5 acid ester

## 2. Scope of claims for patent

Process for production of an optically active  
chrysanthemic acid ester which comprises the first step  
10 comprising reacting a diazomalononic acid diester with 2,5-  
dimethyl-2,4-hexadiene in the presence of a copper complex  
having an asymmetric ligand to produce an optically active  
2,2-dimethyl-3-(2-methylpropenyl)cyclopropane-1,1-  
dicarboxylic acid diester and the second step comprising  
15 conducting partial hydrolysis reaction of the above-  
mentioned optically active dicarboxylic acid diester  
followed by conducting decarboxylation reaction to produce  
an optically active chrysanthemic acid ester.

## 3. Detailed Description of the Invention

20 The present invention relates to a process for  
asymmetric production of chrysanthemic acid ester.

For more detail, the present invention is a process  
for production of an optically active chrysanthemic acid  
ester which comprises the first step comprising reacting a  
25 diazomalononic acid diester with 2,5-dimethyl-2,4-hexadiene

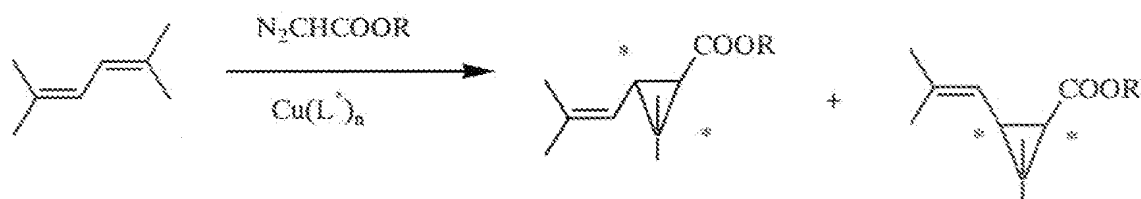
in the presence of a copper complex having an asymmetric ligand to produce an optically active 2,2-dimethyl-3-(2-methylpropenyl)cyclopropane-1,1-dicarboxylic acid diester and the second step comprising conducting partial hydrolysis reaction of the above-mentioned optically active dicarboxylic acid diester followed by conducting decarboxylation reaction to produce an optically active chrysanthemic acid ester.

2,2-dimethyl-3-(2-methylpropenyl)cyclopropane-1-carboxylic acid diester (hereinafter, referred to as the chrysanthemic acid) is an important material as a raw material of synthesized pyrethroid type insecticides, and since it has two asymmetric carbons within a molecule, there are four stereoisomers of d-trans, l-trans, d-cis and l-cis isomers. Among them, it has been known that d-trans and d-cis isomers are especially effective as the raw materials of insecticides. The chrysanthemic acid which can be obtained from natural pyrethrum has a trans-structure.

Two methods are considered to produce an optically active chrysanthemic acid using synthetic method. One is a method comprising conducting the optical resolution of racemic body once produced and the other is a method comprising conducting directly asymmetric synthesis of it.

The present inventors have been confirmed in studied

of the asymmetric synthesis of the chrysanthemic acid ester, and we have ever found that a process for production of an optically active chrysanthemic acid ester comprising reacting a diazoacetate with 2,5-dimethyl-2,4-hexadiene in the presence of a copper complex having an asymmetric ligand.



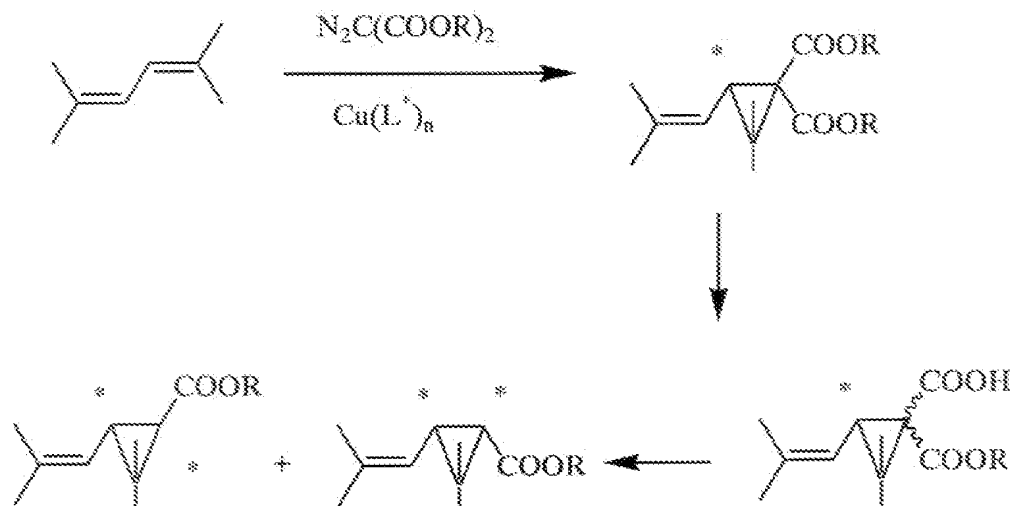
However, in the former invention, an object of selectively producing only desired one kind among four kinds of stereoisomers of chrysanthemic acid was not necessarily achieved, since in this case, the chrysanthemic acid ester was always produced in a form of mixture of trans and cis isomers and even if an asymmetric synthesis of d-isomer is succeeded for trans isomer, it is difficult to predict if excess d-isomer is obtained or excess l-isomer is obtained for cis-isomer.

If the asymmetric synthesis of a combination of d-trans and l-cis isomers can be achieved, this method can become an important process for stereoselective production of only d-trans isomer, since l-cis isomer can be easily derived to d-trans isomer by epimerization reaction.

The present inventors focused on these points and have

more intensively studied and, as a result, they completed newly the present invention.

That is, as described above, the present invention is a process for production of an optically active chrysanthemic acid ester which comprises the first step comprising reacting a diazomalononic acid diester with 2,5-dimethyl-2,4-hexadiene in the presence of a copper complex having an asymmetric ligand to produce an optically active 2,2-dimethyl-3-(2-methylpropenyl)cyclopropane-1,1-dicarboxylic acid diester and the second step comprising conducting partial hydrolysis reaction of the above-mentioned optically active dicarboxylic acid diester followed by conducting decarboxylation reaction to produce an optically active chrysanthemic acid ester.



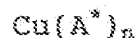
The method for conducting the present invention will be illustrated in detail.

In the first step comprising reacting a diazomalononic acid diester with 2,5-dimethyl-2,4-hexadiene in the presence of a copper complex having an asymmetric ligand to produce an optically active 2,2-dimethyl-3-(2-methylpropenyl)cyclopropane-1,1-dicarboxylic acid diester, the asymmetric ligand of the asymmetric copper complex used as the catalyst is not particularly limited as far as it has an asymmetric structure and is a neutral molecule or ion having an ability of coordinating to copper or copper ion. Examples of the atom coordinating to copper atom include nitrogen, phosphorous, arsenic, antimony, oxygen, sulfur and selenium, and an asymmetric molecule or ion including at least one or more kind among these coordinating atoms is used as the asymmetric ligand. A copper complex including a ligand or anion having a symmetric structure in addition to the asymmetric ligand is also effective. The copper valance may be any of 0, 1 and 2. In actually conducting the reaction, the copper complex may be soluble and insoluble in the reaction system. The catalyst recovered and purified by adequate methods can be used again.

The asymmetric copper complex used as the catalyst and the asymmetric ligand thereof in the first step will be further illustrated.

Among complexes including divalent copper, an

asymmetric complex represented by the below formula:



wherein A is an anion having an asymmetric structure and the charge is generally -1 or -2 and n is representatively 2 or 1 depending on it, , is especially effective. The complex having two kinds of anion whose charge is -1 is also effective.

The anion having the asymmetric structure is not particularly limited, and it is convenient that the conjugated base of following compounds is used.

Examples of these compound include  $\beta$ -dicarbonyl compound,  $\beta$ -ketoimine, oximine, aminoalcohol, amino acid, and carboxylic acid all which have an asymmetric structure.

Among the above-mentioned asymmetric oximines, a Schiff base derived from an asymmetric primary amine and salicylaldehyde derivative is especially superior.

The alcohol part of the diazomalonic acid diester used in the first step is not particularly limited, and a lower aliphatic alcohol is generally used.

The method of the first step can be conducted in the absence of a solvent and in 2,5-dimethyl-2,4-hexadiene and conducted by diluting a suitable solvent.

The reaction temperature in conducting the method of the first step is not particularly limited, and a range of -50°C to 150°C is usually suitable. Especially, in the

case of conducting reaction at a melting point (15°C) of 2,5-dimethyl-2,4-hexadiene or less, a suitable solvent is preferably added to the reaction system. Examples of the suitable solvent include an alkyl-substituted benzene derivative such as toluene.

Next, among the method of the present invention, the second step comprising producing an optically active chrysanthemic acid ester from 2,2-dimethyl-3-(2-methylpropenyl)cyclopropane-1,1-dicarboxylic acid diester will be illustrated.

Methods for producing an optically inactive chrysanthemic acid ester from an optically inactive dicarboxylic acid diester described above have been known (Bull. Soc. Chim. France, 1411 (1967)).

The present step is usually carried out by next two steps reaction. That is, the first reaction comprising hydrolyzing the above-mentioned optically active dicarboxylic acid diester partially to derive to the optically active 2,2-dimethyl-3-(2-methylpropenyl)cyclopropane-1,1-dicarboxylic acid monoester and the second reaction comprising conducting decarboxylation of the above-mentioned optically active dicarboxylic acid monoester to derive to the optically active chrysanthemic acid ester.

The method using for the first partial hydrolysis

reaction is not particularly limited, and heating in water or a suitable water-containing solvent and in the presence of an alkali such as sodium hydroxide and potassium hydroxide is usually convenient.

5       The method using for the second decarboxylation reaction is not particularly limited, and the method comprising heating with an amine such as quinoline, 2,2'-bipyridyl and 1,10-phenanthrene in the presence of a catalyst such as copper powder, an inorganic copper salt or  
10       an organic copper salt is usually conducted.

      The present invention will be illustrated in more detail by way of Examples, but off course, the present invention is not limited by these Examples.

15       Example 1

          First step

          3.7 g of copper bis[N-S- $\alpha$ -phenyl- $\beta$ -(p-tolyl)ethyl-salicylaldehydato] was dissolved in 35 g of 2,5-dimethyl-2,4-hexadiene and a mixture of 20 g of diethyl  
20       diazomalonate and 24 g of the above-mentioned diene was added dropwise thereto over 12 hours. The reaction was conducted with enough stirring under an atmosphere of nitrogen and at first, by heating to 90°C until starting to generate nitrogen gas and then the reaction temperature was  
25       kept at 50°C. After detecting generating no nitrogen gas,



unreacted diene was removed by distillation from the reaction mixture under reduced pressure. The residue was further distilled under reduced pressure to obtain 17 g of diethyl 2,2-dimethyl-3-(2-methylpropenyl)cyclopropane-1,1-dicarboxylate at boiling point 100°C/2 mmHg as an oily product (Yield: 59%). Optical rotation  $\alpha_D$  was  $-0.46^\circ$ ,  $\alpha_{436}$  was  $-1.20^\circ$  and  $\alpha_{365}$  was  $-2.34^\circ$  (not dilute, 1 dm).

#### Second step

##### (1) Partial hydrolysis reaction

16.5 g of dicarboxylic acid diester obtained in the first step and 4.0 g of potassium hydroxide were dissolved in a solution of 100 ml of water and 100 ml of ethanol, and the mixture was heated and stirred under reflux for 7 hours. Ethanol was removed by distillation from the reaction mixture and then, the acidic product was extracted with ether. The extract was dried over sodium sulfate and then, ether was removed by distillation under reduced pressure to obtain 12.9 g of 2,2-dimethyl-3-(2-methylpropenyl)cyclopropane-1,1-dicarboxylic acid monoethyl ester as an oily material (Yield: 87%). Optical rotation  $\alpha_D$  was  $-0.29^\circ$ ,  $\alpha_{546}$  was  $-0.38^\circ$  and  $\alpha_{436}$  was  $-0.87^\circ$  (not dilute, 1 dm).

##### (2) Decarboxylation reaction

11.8 g of the dicarboxylic acid monoester obtained in the above reaction was dissolved in 20 ml of

benzene and the resultant was added dropwise over about 1 hour into a mixture of 2.0 g of copper powder and 50 g of quinoline which kept at about 200°C. Stirring was further continued at the same temperature for 1 hour and generation of carbon dioxide was not detected. The reaction mixture was cooled and then, acidified by dilute hydrochloric acid and the neutral product was extracted with ether. the extract was washed with dilute alkali and water, and then, dried over sodium sulfate. The residue obtained by removing ether by distillation from it was further distilled under reduced pressure to obtain 6.3 g of an oily product at boiling point 40°C to 60°C/2 mmHg. This product was analyzed by gas chromatography, IR, NMR and MS to confirm a mixture comprising trans isomer of ethyl chrysanthemate (34%), cis isomer of ethyl chrysanthemate (31%) and unknown neutral material (35%). Optical rotation showed  $\alpha_D +0.38^\circ$  (not dilute, 1 dm) as mixture.

This sample was hydrolyzed and trans-chrysanthemic acid obtained was isolated and purified. Optical rotation  $[\alpha]_D$  showed  $\alpha_D +0.35^\circ$  (c8.0, chloroform) as mixture.



特 許 願

昭和47年10月26日

特許庁長官 三宅幸夫殿

1. 発明の名称

第一萜酸エステルの不整合合成法

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⑬ 日本国特許庁

公開特許公報

⑪特開昭 49-66660

⑬公開日 昭49.(1974) 6. 27

⑫特願昭 47-107722

⑭出願日 昭47.(1972)10.26

審査請求 未請求 (全4頁)

庁内整理番号

⑮日本分類

6742 43

16 C86

6939 4A

13M0421.1

6512 4A

13M01

7308 4A

13M02

明 細 書

1. 発明の名称

第一萜酸エステルの不整合合成法

2. 発明の要旨

不飽和な配位子を有する錯体の存在下に、ジメチルマロン酸ジエステルと、γ-ジメチル-2,4-ヘキサジエンとを反応させ、光学活性な2,γ-ジメチル-3-(2-メチルプロペニル)シクロプロパン-1,1-ジカルボン酸ジエステルを製造する第一工程および光学活性な上記ジカルボン酸ジエステルを部分加水分解反応について脱炭酸反応させて光学活性な第一萜酸エステルを製造する第二工程よりなることを特徴とする光学活性第一萜酸エステルの製造方法。

3. 発明の詳細な説明

本発明は第一萜酸エステルの不整合合成法に関するものである。

さらに詳しくいえば、本発明は不飽和な配位子を有する錯体の存在下に、ジメチルマロン

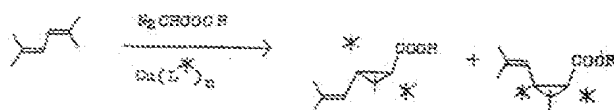
酸ジエステルと、γ-ジメチル-2,4-ヘキサジエンとを反応させ、光学活性な2,γ-ジメチル-3-(2-メチルプロペニル)シクロプロパン-1,1-ジカルボン酸ジエステルを製造する第一工程および光学活性な上記ジカルボン酸ジエステルを部分加水分解反応について脱炭酸反応させて、光学活性な第一萜酸エステルを製造する第二工程よりなることを特徴とする光学活性第一萜酸エステルの製造方法である。

2,γ-ジメチル-3-(2-メチルプロペニル)シクロプロパン-1,1-ジカルボン酸(以下第一萜酸という)は合成ピレスロイド系殺虫剤の原料として重要な物質であるが、一分子中に2個の不飽和基を有しており、ためにエートランス、メートランス、メーシスおよびローシスの4種の立体異性体として存在する。これらのうち、殺虫剤の原料としては、メートランス体およびローシス体が特に有効であることが知られている。また天然の除虫薬とも得られる第一

明瞭なエートランス構造を有している。

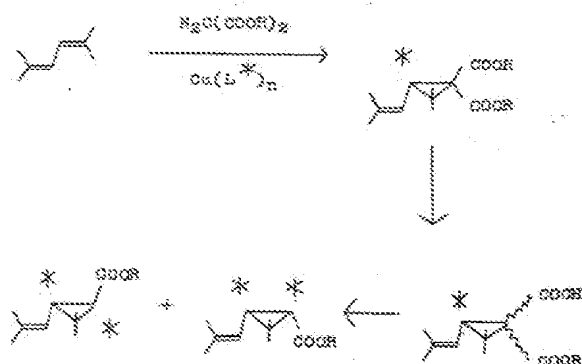
合成的手法により光学活性第一基質を得るには二つの方法が考えられる。一つは一基合成し、その二基を光学分割するものであり、いそ一つは直接不斉合成する方法である。

本発明者らはかねてから第一基質エニタールの不斉合成法について研究を重ねてきたが、先般不斉配位子を有する錯体の存在下で、ジマゾロン酸ジエステルと、 $\gamma$ -ブチロラクトン、 $\gamma$ -ブチロラクトンとを反応させることを特許とする光学活性第一基質エニタールの製造方法（以下本発明という）を見出した。



しかしながら本発明の方法においては、第一基質の四種の立体異性体のうち、希望する唯一種のもののみを選択的に合成するという目的は

エニタール（ $\gamma$ -ブチロラクトン）シクロプロパン、 $\gamma$ -ブチロラクトンジエステルを製造する第一工程および光学活性上記ジマゾロン酸ジエステルを部分加水分解反応、ついで脱保護反応を経て、光学活性第一基質エニタールを製造する第二工程よりなることを特許とする光学活性第一基質エニタールの製造方法である。



必ずしも達成されなかった。というのはこの場合、生成する第一基質エニタールはエートランス体とシス体の混合物であって、しかもたとえエートランス体については二種の不斉合成に成功しても、シス体については二種の不斉合成に成功するかが、二種が得られるか、予断が許されなかったからである。

ところがもしエートランス体とシス体の混合物の不斉合成が達成できれば、これはエートランス体のみを立体選択的に合成する有力な方法とせらる。というのはシス体はエニタール反応により容易にエートランス体に変換することが出来るからである。

このような点に着目して、本発明者らはさらに研究を重ねた結果、新たに本発明を完成することになった。

すなわち、本発明は前記のように、不斉配位子を有する錯体の存在下で、ジマゾロン酸ジエステルと、 $\gamma$ -ブチロラクトン、 $\gamma$ -ブチロラクトンとを反応させ、光学活性第一、二

本発明を実施する方法について詳細に説明する。

まず不斉配位子を有する錯体の存在下で、ジマゾロン酸ジエステルと、 $\gamma$ -ブチロラクトン、 $\gamma$ -ブチロラクトンとの反応を行ない、光学活性第一、二（エニタールプロパニル）シクロプロパン、 $\gamma$ -ブチロラクトンジエステルを製造する第一工程において、触媒として用いられる不斉配位子の不斉配位子としては、不斉な構造をもち、しかも銅あるいは銀イオンに配位する能力のある中性分子またはイオンであるものが特に好ましい。銅に対する配位原子としてはたとえば、酸素、リン、ヒソ、マンチオン、硫黄、イオウ、セレンなどをあげることができ、これらの配位原子のうち少なくとも一種以上をふくむ不斉な分子またはイオンが不斉配位子として用いられる。また不斉配位子と同時に触媒構造を有する配位子あるいは錯イオンをふくむ錯体を有効である。銅の原子価に照しては、 $\gamma$ -ブチロラ

000000-000000

反応は強熱を要せず、十分攪拌して行ない、反応温度については最初発生ガスの発生が始まるまでは $70^{\circ}\text{C}$ まで加熱したが、その後は $50^{\circ}\text{C}$ に保った。もはや発生ガスの発生が認められなくなった後、反応混合物より未反応のジエンを減圧下に留去した。残留物をさらに減圧で蒸留すると、沸点 $100^{\circ}\text{C}/2\text{mmHg}$ で2, ユージオチル-3-(2-メチルプロペニル)シクロプロパン-1, ノージカルボン酸ジエチル/7.7 (収率5.4%) が油状生成物として得られた。折光率は $n_D^{20}=1.464$ ,  $n_D^{25}=1.458$ ,  $n_D^{30}=1.452$  (無希釈、/40) であった。

## 第二工程

### (1) 部分加水分解反応

第一工程で得たシカルボン酸ジエチル/11.8gおよび水酸化カリウム4.0gを、水100ccおよびエタノール100ccの溶液にとり、混合物を室温下、7時間加熱攪拌した。反応混合物よりエタノール

を減圧留去した残留物をさらに減圧蒸留すると沸点 $80^{\circ}\text{C}-85^{\circ}\text{C}/2\text{mmHg}$ で油状生成物4.5gが得られた。このものは第一希酸エチルのトランス体(3.4%)、シス体(3.1%)および未知中性物質(3.5%)よりなる混合物であることが、ガスクロマトグラフィー、IR、NMRおよびMSより判明した。折光率は混合物のため、 $n_D^{20}+0.389$  (無希釈、/40) を示した。

なおこのサンプルを加水分解し、得られたトランス-第一希酸を単離、精製すると折光率 $(n_D^{20})+0.350$  ( $n_D^{25}=0.340$ , クロロホルム)を示した。

特別 昭和41-88880(4) ールを減圧で留去した後、残留生成物をエーテルで抽出した。抽出液を蒸留で乾燥後、エーテルを減圧留去すると2, ユージオチル-3-(2-メチルプロペニル)シクロプロパン-1, ノージカルボン酸モノエチル/2.4g (収率5.7%) が油状物として得られた。折光率は $n_D^{20}=1.458$ ,  $n_D^{25}=1.452$ ,  $n_D^{30}=1.446$  (無希釈、/40) であった。

### (2) 脱炭酸反応

先の反応で得たシカルボン酸モノエチル/11.8gをベンゼン20ccにとり、これを約 $200^{\circ}\text{C}$ に保った加熱管2.0gとキノリン5.0gの混合物中へ、約1時間かけて滴下した。さらに1時間間隔で攪拌をつづけると、もはや炭酸ガスの発生は認められなかった。反応混合物を冷却後、希硫酸で酸性とし、中性生成物をエーテルで抽出した。抽出液を希アルカリおよび水で洗滌したのち、蒸留で乾燥し

## 5. 添付書類の目録

- |         |       |
|---------|-------|
| (1) 明細書 | 1通/1頁 |
| (2) 委任状 | 1通    |

## 6. 前記以外の発明者、特許出願人または代理人

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